UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/875,849	09/08/1997	MICHAEL J. BRISKIN	1855.1004-002 (MPI1995-01	4411

23630 7590 12/24/2008

MCDERMOTT WILL & EMERY LLP
28 STATE STREET
BOSTON, MA 02109-1775

EXAMINER	
SCHWADRON, RONALD B	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
12/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MICHAEL J. BRISKIN, DOUGLAS J. RINGLER,
DOMINIC PICARELLA, and WALTER NEWMAN

Appeal 2008-2656
Application 08/875,849
Technology Center 1600

Decided: December 23, 2008

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and MELANIE L. MCCOLLUM, Administrative *Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 24-26, 28-32, 105-108, 111-113, 115, 116, 118-121, 124-150, and 152-160. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

The claims in this appeal are directed to a fusion protein comprising a naturally occurring primate MAdCAM polypeptide.

MAdCAM is the acronym for "Mucosal Addressin Cell Adhesion Molecule-1," an adhesion receptor for lymphocytes (Spec. 3: 4-6). In the mouse, MAdCAM is expressed in mucosal vascular endothelial cells, including Peyer's patches and the lamina propria of the small and large intestines (*id.* at 3: 9-14). MAdCAM specifically binds to the lymphocyte integrin α4β7 receptor which mediates lymphocyte homing to the Peyer's patches in the gut (*id.* at 3: 24-27; at 4: 25-30).

Claims 24-26, 28-32, 105-108, 111-113, 115, 116, 118-121, 124-150, and 152-160 are appealed (App. Br.[1] 4). The claims stand finally rejected by the Examiner as follows:

Claims 24-26, 28-32, 105-108, 111-113, 115, 116, 118-121, 124, 125, 136-150, and 152-160 under 35 U.S.C. § 112, first paragraph as lacking written description in the Specification (Ans.[2] 3-4);

Claims 24-26, 28-31, 105-108, 111, 113, 115, 116, 118, 120, 121, 124, 126-142, 144-147, 149, 150, 152, 154, 155, and 157-160 under 35 U.S.C. § 103(a) as obvious over Butcher (WO 94/13312, published Jun. 23, 1994), Vonderheide (U. S. Pat. No. 5,599,676, issued Feb. 4, 1997) and Erle ("Expression and Function of the MadCAM-1 Receptor, Intergrin α4β7, on Human Leukocytes," 153 JOURNAL OF IMMUNOLOGY, 518-27, 1994) (Ans. 7); and

[1] Amended Appeal Brief (date stamped Aug. 16, 2006).
[2] Examiner's Answer (mailed Jul. 6, 2007).

Claims 32, 112, 119, 125, 143, 148, 153, and 156 under 35 U.S.C. § 103(a) as obvious over Butcher, Vonderheide, Erle, and Capon (U.S. Pat. No. 5,565,335, issued Oct. 15, 1996) (Ans. 8).

Claim 24, which is representative of the appealed subject matter, reads as follows:

> 24. A fusion protein comprising a naturally occurring primate MAdCAM, wherein said naturally occurring primate MAdCAM binds α4β7 integrin and has at least about 75% amino acid sequence similarity to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6.

WRITTEN DESCRIPTION REJECTION

Claims 24-26, 28-32, 105-18, 11-113, 115, 116, 118-121, 124, 125, 136-150, and 152-160 stand rejected under § 112, first paragraph, as lacking written description in the Specification.

Issue

Claim 24 is directed to a genus of fusion proteins comprising naturally occurring primate MAdCAM polypeptides which bind integrin and have a specifically recited structural motif. This issue is this rejection is as follows:

Does the Specification provide sufficient structural characteristics to identify the claimed genus of naturally occurring primate MAdCAM polypeptides and show that such structure is correlated with the claimed integrin binding activity?

Findings of Fact (FF)

Claim 24

1. Claim 24 is directed to a genus of fusion proteins comprising a naturally occurring primate MAdCAM. The claim requires that the primate MAdCAM:

2. ● is naturally occurring, i.e., is found naturally in primates (Spec. 13:16-20);

3. ● binds α4β7 integrin; and

4. ● has at least about 75% amino acid sequence similarity to an amino acid sequence which is set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:6 ("the structural motif").

5. In sum, the naturally occurring primate MAdCAM of claim 24 is required to have a specific function (FF3) and structural motif (FF4).

Specification

6. The Specification describes three specific naturally occurring primate MAdCAM cDNAs and the polypeptides encoded by them. These include: human MAdCAM-1 clone 4 (Figure 1; SEQ ID NO:2), human MAdCAM-1 clone 20 (Figure 2; SEQ ID NO:4), and macaque MAdCAM-1 (Figure 3; SEQ ID NO:6). *See* Spec. 6:31 to Spec. 7:25; Spec. 17: 18-29.

7. The Specification describes several domains which are characteristic of the disclosed primate MAdCAMs. These include:

8. ● two immunoglobulin-like (Ig-like) domains at the polypeptide's amino terminus which are homologous to the Ig-like integrin binding domains of murine MAdCAM (Spec. 18:22-25; 20:20 to 21:12);

9. ● a GLDTSL motif found in the first Ig-like domain which is conserved and required for integrin binding (Spec. 19:19 to 20:12-33);

10. ● a mucin domain downstream of the Ig-like domains (Spec. 21:13-30); and

11. ● a transmembrane domain (Spec. 22:21-22).

12. These domains are illustrated in Figures 1-3 of the Specification. The positions of the two terminal Ig-like domains are indicated by the boxed cysteine residues; the mucin-like domain is boxed; the transmembrane domain follows the mucin-like domain and is underlined. *See* Spec. 6:31 to Spec. 7:25; Spec. 17:18-29.

13. In sum, the Specification discloses structural features which are characteristic of primate MAdCAM (FF6-12), as well as those structures which appear to be necessary for it to bind α4β7 integrin (FF8-9).

Principles of Law

"The 'written description' requirement [under 35 U.S.C. § 112, first paragraph] implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005).

For claims to a genus of genetic materials, the Federal Circuit has imposed an additional requirement. "[A] generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function." *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

Instead, the written description must define the genus to enable one skilled in the art to "visualize or recognize the identity of the members of the genus," e.g., by providing a description of "structural features commonly possessed by members of the genus that distinguish them from others." *Lilly*, 119 F.3d at 1568.

As noted in *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003), "*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure."

Consistent with *Lilly* and *Amgen*, in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), it was held that a claimed DNA could be described without, necessarily, disclosing its structure. The court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" *See id.* at 964.

Analysis

Based on the principles of law as set forth above, we conclude that claim 24 complies with the written description requirement of § 112, first paragraph. As noted previously, claim 24 involves a naturally occurring primate MAdCAM with specific structural and functional characteristics

(FF1-5). According to the Specification, primate MAdCAM comprises two immunoglobulin-like domains, a mucin domain, and a single transmembrane domain (FF8, 10, 11). The structure of the genus is further limited by sequence similarity to one of three different specifically recited amino acid sequences (FF4). That is, the claimed fusion protein must comprise a MAdCAM which "has at least about 75% amino acid sequence similarity to an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:6" (claim 24). These structural features enable persons of skill in the art to recognize the identity of members of the claimed genus comprising naturally occurring primate MAdCAM polypeptides as required under *Lilly* and *Amgen*.

There is also a correlation between the structure of the claimed polypeptide and its claimed function to be bind α4β7 integrin. The Specification clearly teaches domains and amino acid motifs within these domains which are necessary to conserve MAdCAM's integrin binding activity (FF8, 9). Thus, there is a specific teaching in the Specification about the relationship between the disclosed integrin binding activity and the structure of the claimed polypeptide, fulfilling the necessary written descriptive support for the claimed genus as articulated in *Amgen*, 314 F.3d at 1332 and others.

For the foregoing reasons, we reverse the rejection of the claims 24-26, 28-32, 105-18, 11-113, 115, 116, 118-121, 124, 125, 136-150, and 152-160.

OBVIOUSNESS REJECTION

1. Claims 24-26, 28-31, 105-108, 111, 113, 115, 116, 118, 120, 121, 124, 126-142, 144-147, 149, 150, 152, 154, 155, and 157-160 stand rejected under 35 U.S.C. § 103(a) as obvious over Butcher, Vonderheide, and Erle.

Issue

Is a naturally occurring primate MAdCAM having the functional and structural characteristics recited in claim 24 an obvious product of Vonderheide's method?

Findings of Fact

Scope and content of the prior art

The Butcher patent

14. Butcher describes the cDNA and amino acid sequence of murine MAdCAM-1 (Butcher, at 3, ll. 11-12; at 4, ll. 25-26).

15. Butcher teaches that murine MAdCAM can be joined to an immunoglobulin constant region to produce a fusion protein with an enhanced lifetime when administered in vivo (Butcher, at 7, ll. 11-13; Ans. 7).

Erle

16. Erle detects expression of human α4β7 integrin in human blood cells using anti-α4β7 antibody (Erle, Abstract; at 519-520; Figure 1 ("anti-α4β7 mAb Act-1").

17. Human α4β7 (as expressed in lymphoma cell lines) is able to adhere to FN38, a subunit of fibronectin (Erle, at ¶ spanning cols. 1 to 2 on 521).

18. To determine whether human α4β7 could also mediate adhesion to MAdCAM-1, cell lines genetically engineered to express murine MAdCAM-1 were utilized (Erle, at 521, 1st full ¶).

19. "Because the human homologue of MAdCAM-1 has not yet been identified, we used transfectants expressing murine MAdCAM-1 in our experiments" (Erle, at 525). Erle states that it was expected that murine MAdCAM-1 would have the same adhesion properties as the human homolog (*id.*).

20. Murine MAdCAM-1 is expressed mucosal lymphoid organ HEV and on gut lamina propria (Erle, at 518).

The Vonderheide patent

21. Vonderheide teaches methods for isolating novel nucleic acids encoding receptors for α4 integrins, including the receptor for α4β7 integrin (Vonderheide, at col. 4, ll. 27-32; at col. 6, ll. 6-21; Abstract).

22. Generally, the methods are described as "functional cloning" because they are based on the functional interaction (i.e., adhesion) of α4 integrin with its receptor (Vonderheide, at col. 6, ll. 10-20; col. 25, l. 25 to col. 27, l. 61).

Difference between the prior art and the claimed invention

23. Claim 24 directed to a genus of naturally occurring primate MAdCAMs which bind α4β7 integrin (FF1-3) and which have at least about 75% amino acid sequence similarity to an amino acid sequence which is SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:6, each of which is a primate MAdCAM represented by a specific sequence of amino acids (FF4).

24. The Butcher teaches a murine MAdCAM (FF14).

25. Murine MAdCAM has less than about 75% amino acid sequence similarity with macaque and human MAdCAM (Spec. 58: 9-12), the representative primate MAdCAMs described in the Specification.

26. "Initial attempts to clone the human homologue to murine MAdCAM-1 by low stringency cross-hybridization suggested that nucleotide conservation between murine MAdCAM-1 and higher species was poor" (Shyjan, 2851 THE J. IMMUNOL. 2853, 1996).

Principles of Law

> Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon*, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985).
>
> We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to

> achieve the claimed invention" was also required. *Id.* (citing *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984)).
>
> That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in KSR. While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. . . . Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd., 492 F3d 1350, 1357 (Fed. Cir. 2007).

> The Supreme Court's analysis in KSR thus relies on several assumptions about the prior art landscape. First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See *Takeda*, 492 F.3d at 1357 ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained

> that this "easily traversed, small and finite number of alternatives ... might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.
>
> In other words, post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.

Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008).

Analysis

The Examiner's position is that it would have been obvious to persons of ordinary skill in the art to have utilized Vonderheide's method of cloning the α4β7 integrin receptor (FF21-22) to have cloned a primate MAdCAM having the characteristics recited in claim 24 (Ans. 8). The Examiner finds that there would have been a reasonable expectation of success because Erle teaches the materials (FF16-18) that would be utilized in Vonderheide's functional cloning method (Ans. 16) and Vonderheide teaches that its method has had success in cloning other α4β7 integrin receptors (Ans. 19). The issue in this rejection is whether a primate MAdCAM having the functional and structural characteristics recited in claim 24 would have been the expected product of Vonderheide's method.

In making an obviousness determination, all the limitations in a claim must be addressed. Here, claim 24 is directed to a fusion protein comprising a genus of naturally occurring primate MAdCAMs which have α4β7 activity and 75% amino acid sequence similarity to one of three specifically recited primate amino acid sequences. While precise teachings that would have led persons of ordinary skill in the art to have made the claimed invention are not needed, "it remains necessary to identify some reason that would have

led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d at 1357. Polypeptides are, of course, chemical compounds. The Examiner has not articulated a reason nor provided any teachings that would have led the skilled worker to have modified Butcher's murine MAdCAM sequence (FF14) to have arrived at a primate MAdCAM with the recited structural motif. Thus, the Examiner has not set forth a prima facie case that a primate MAdCAM with 75% sequence similarity to SEQ ID NOS: 2, 4, and 6 would have been obvious to persons of ordinary skill in the art.

Unlike in *Ex parte Kubin*, 83 USPQ2d 1410 (BPAI 2007), there is no evidence that a species that falls within the scope of claim 24 would have been obvious to persons of ordinary skill in the art. Vonderheide's methods rely on the functional interaction between the α4 integrin to its receptor (FF22), i.e., α4β7 integrin and the receptor polypeptide to which adheres. There is evidence of record that α4β7 is also able to adhere to fibronectin (FF17). Vonderheide's functional cloning method applied to α4β7 could just as well have captured fibronectin. Consequently, the existence of the materials to have carried out Vonderheide's method (Ans. 16, 19) would not have "put[ ] a person having ordinary skill in possession of the key to success" to have arrived at a MAdCAM sequence within the scope of claim 24. *See Ex parte Goldgaber*, 41 USPQ2d 1172, 1174 (BPAI 1995) (involving the patentability of a DNA coding for a beta-amyloid protein). *See also* FF26.

For the foregoing reasons, we reverse the obviousness rejection of claims 24-26, 28-31, 105-108, 111, 113, 115, 116, 118, 120, 121, 124, 126-142, 144-147, 149, 150, 152, 154, 155, and 157-160.

2. Claims 32, 112, 119, 125, 143, 148, 153, and 156 under 35 U.S.C. § 103(a) stand rejected as obvious over Butcher, Vonderheide, Erle, and Capon (Ans. 8).

Capon is cited by the Examiner for its teaching of homodimers as recited in claim 32 and others (Ans. 9). As Capon does not address the deficiencies of the prior art as discussed above, we reverse this rejection, as well.

CONCLUSIONS OF LAW

The Specification provides sufficient structural characteristics to identify the claimed genus of naturally occurring primate MAdCAM polypeptides and shows that such structure is correlated with the claimed integrin binding activity. Thus, we reverse the rejection of claims 24-26, 28-32, 105-18, 11-113, 115, 116, 118-121, 124, 125, 136-150, and 152-160 under § 112, first paragraph.

The claimed naturally occurring primate MAdCAM having the functional and structural characteristics recited in claim 24 would not have been an obvious product of Vonderheide's method. For this reason, we reverse the rejection of claims 24-26, 28-32, 105-108, 111-113, 115, 116, 118-121, 124-150, and 152-160 under 35 U.S.C. § 103(a).

REVERSED

dm

Hamilton, Brook, Smith & Reynolds, P.C.
530 Virginia Road
P.O. Box 9133
Concord, MA 01742-9133